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EXAMINER	
LUNDGREN, JEFFREY S	
ART UNIT	PAPER NUMBER
1639	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/563,077	NOBLE ET AL.	
	Examiner	Art Unit	
	JEFFREY S. LUNDGREN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) *3 and 4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/6/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of the species "schizophrenia" in the reply filed on February 14, 2008, is acknowledged. The traversal is on the grounds that the species are each linked by a common inventive concept. This is not found persuasive because the claims lack a special technical feature as evidenced by the art-based rejection below (*i.e.*, claim 1 has been found to be obvious over the art).

The requirement is still deemed proper and is therefore made FINAL. Accordingly, claims 1, 2, 5 and 6 are treated on the merits, and claims 3 and 4 are withdrawn as being directed to non-elected species. Should this application present a claim generic to the withdrawn species that is found to be allowable, the claims will be rejoined.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on September 6, 2006, has been considered by the Examiner. The submission is in compliance with the provisions of 37 CFR § 1.97. Enclosed with this Office Action is a return-copy of the Form PTO-1449 with the Examiner's initials and signature indicating those references that have been considered.

Claim Rejections - 35 USC § 112, first paragraph – New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5 and 6, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for containing new matter. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claim 1 contains new matter for reciting the limitation:

> "an ***A1+*** genotype is indicative of a candidate for treatment with ***low dose*** DRD2 binding atypical antipsychotics and/or SSRIs that increase D2 dopamine receptor density;"

and the limitation:

> "an ***A1-*** genotype is indicative of a candidate for treatment with high dose D2 dopamine receptor binding atypical antipsychotics or alternative antidepressant."

These limitations are in direct contradiction to Applicants provisional application (see first paragraph under Summary of the Invention on page 1; see also claim 1 on page 53), their published International Application WO 2005/007871 A2 (paragraph 0004), and the current specification. Specifically, the specification states:

> "The invention provides methods of identifying candidate psychiatric patients or patients with movement disorder for treatment with medication that acts at the D2 dopamine receptor. The method comprises determining a patient's D2 dopamine receptor DRD2) genotype. Patients having the Taq1A (A1) allele (***A1+ allelic status) are candidates for treatment with high dose of high D2 dopamine receptor binding antipsychotics*** and/or SSRIs that influence D2 dopamine receptor density. Patients lacking the Taq1A allele (***A1- allelic status) are not likely to respond well to these SSRIs, and are candidates for treatment with lowdose of low D2 dopamine receptor binding or low dose high D2 dopamine receptor binding atypical antipsychotics***."

Specification, paragraph 0004 (emphasis added).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 2, 5 and 6, are rejected under 35 U.S.C. § 101 because the claims do not constitute statutory subject matter.

Claims 1, 2, 5 and 6, are drawn to a method for determining persons that are candidates treatment based on their genetic profile. A statutory process must include a step of a physical

transformation, or produce a useful, concrete, and tangible result. *See State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600-1601 (Fed. Cir. 1998). *See also AT&T Corp. v. Excel Communications Inc.*, 50 USPQ2d 1447 (Fed. Cir. 1999). The instant claims do not result in a physical transformation, thus the Examiner must determine if the instant claims include a useful, concrete, and tangible result. In determining if the claimed subject matter produces a useful, concrete, and tangible result, the Examiner must determine each standard individually. For a claim to be "useful" the claim must produce a result that is specific and substantial. For a claim to be "concrete" the process must have a result that is reproducible. For a claim to be "tangible" the process must produce a real world result.

As noted from *State Street Bank*, the statutory category of the claimed subject matter is not relevant to a determination of whether the claimed subject matter produces a useful, concrete, and tangible result:

> "The question of whether a claim encompasses statutory subject matter should not focus on *which* of the four categories of subject matter a claim is directed to -- process, machine, manufacture, or composition of matter--but rather on the essential characteristics of the subject matter, in particular, its practical utility. Section 101 specifies that statutory subject matter must also satisfy the other "conditions and requirements" of Title 35, including novelty, nonobviousness, and adequacy of disclosure and notice. *See In re Warmerdam*, 33 F.3d 1354, 1359, 31 USPQ2d 1754, 1757-58 (Fed. Cir. 1994). For purpose of our analysis, as noted above, claim 1 is directed to a machine programmed with the Hub and Spoke software and admittedly produces a "useful, concrete, and tangible result." *Alappat*, (33 F.3d at 1544, 31 USPQ2d at 1557). This renders it statutory subject matter, even if the useful result is expressed in numbers, such as price, profit, percentage, cost, or loss."

State Street Bank & Trust Co. v. Signature Financial Group Inc., 47 USPQ2d 1596, at 1602 (Fed. Cir. 1998).

In the instant case, claims 1, 2, 5 and 6, do not require production of a tangible result. The current claims read on scanning pre-obtained genetic data and making a classification, and do not require any physical transformation. A tangible result requires that the claim must set forth a practical application to produce a real-world result. This rejection could be overcome by amendment of the claims to recite that, for example, an actual drug or medication is administered, or that tissues are collected and analyzed for genotype assignment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2 and 5, are obvious over Suzuki #1, Suzuki #2 and Turrone:

Claims 1, 2 and 5, are rejected under 35 U.S.C. § 103(a) as being unpatentable over Suzuki *et al.*, *Pharmacogenetics 10(4)*:335-341 (**2001**)[1] (hereinafter "Suzuki #1"), in view of Suzuki *et al.*, *Am. J. Psychiatry 158(10)*:1714-1716 (**2001**) (hereinafter "Suzuki #2"), and Turrone *et al.*, *Am. J. Psychiatry 159(1)*:133-135 (**2002**).

Claim 1 is directed to a method for identifying a candidate psychiatric patient for treatment with antipsychotic or antidepressant medication that acts on DRD2, comprising determine the A1+ genotype, wherein an A1+ genotype is indicative of a candidate for treatment with low dose DRD2 binding atypical antipsychotics and/or SSRIs that increase D2 dopamine receptor density; and an A1- genotype is indicative of a candidate for treatment with high dose D2 dopamine receptor binding atypical antipsychotics or alternative antidepressant.

It is known that the human DRD2 gene contains a *Taq*I restriction fragment, and that persons having at least one A1 allele show lower DRD2 density in the striatum and caudate

nuclei, with diminished dopaminergic activity and reduced glucose metabolism in brain regions with abundant dopamine receptors (Suzuki #1, pages 2 and 3). Suzuki #1 describes the basis for his study on understanding the differences between clozapine and nemonapride and their potential for therapeutic treatment based on *TaqI*A polymorphism:

> "Based on these data of the lower density and reduced function of DRD2 in the subjects with *A1* alleles, the DRD2 occupancy in neuroleptic-treated schizophrenic patients with *A1* alleles may be different from that in patients with no *A1* allele. This leads to the hypothesis that the *Taq1* A polymorphism is related to therapeutic response to antipsychotic drugs in the treatment of schizophrenia."

Introduction, last two sentences of the third paragraph; and:

> "In addition, clozapine has a relatively weak affinity for DRD2 compared with a strong binding activity for 5-HT2A, 5-HT2C, acetylcholine and histamine receptors (Schotte et al., 1995). Therefore, a study design using a fixed-dose of a selective DRD2 antagonist is preferable to clarify the association between DRD2 polymorphisms and neuroleptic response."

Introduction, last two sentences of the fourth paragraph.

In the study, Suzuki #1 reports the results wherein candidate psychiatric patients having the *Taq*I geneotype was determined as either A1 positive or A1 negative, and studied their response to nemonapride. Suzuki observed that the A1+ patients responded better to treatment for schizophrenia (as in claim 2) using nemonapride than those patients that that were A1- (see *Discussion* on pages 6-8, see especially the third and fourth paragraphs in this section). Suzuki #1 states:

> "In conclusion, the present results suggest that the *Taq1* A DRD2 polymorphism is related to an early therapeutic response to nemonapride in schizophrenic patients, possibly by modifying the efficiency of DRD2 antagonism of the drug in the central nervous system. The identification of the *Taq1* A DRD2 genotypes may be a pharmacodynamic marker for the prediction of therapeutic effects of antipsychotic agents before initiating drug treatment."

Suzuki #1, page 8, final paragraph.

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[1] The copy of this reference was provided by Applicants from an HTML source; accordingly, the pages as printed (10 pages from the website) do not correspond to the published journal pages.

Although Suzuki #1 generally teaches that schizophrenic patients having the A1+ allele are candidates for nemonapride treatment, and that nemonapride affects the plasma levels of prolactin, it is not explicitly taught in the reference to use a "low dose" or "high dose" drug based on A1+ allele (as in claim 1), or that risperidone is such a compound (as in claim 5).

Suzuki #2 is similarly related, and discloses the results of a clinical study that determined the effects of nemonapride on patients with TaqI A polymorphism. Suzuki #2 found:

> "We recently reported that ***patients with schizophrenia who had the A1 allele showed greater prolactin response*** (16) and better therapeutic response (17) to nemonapride, a selective dopamine antagonist, than patients without this allele. These findings indicate that A1 carriers show higher DRD2 blockade by neuroleptic drugs than noncarriers."

Suzuki #2, page 1715, paragraph bridging cols. 1 and 2 (emphasis added); and:

> "***A possible clinical implication of our findings are that A1 carriers could receive potentially lower doses of neuroleptics if this polymorphism were used in a pharmacogenomic screening procedure***."

Suzuki, page 1715, col. 2, last paragraph (emphasis added).

Turrone teaches that clozapine, unlike typical antipsychotics, does not elevate prolactin levels, and has important pharmacodynamics different than risperidone (page 133, col. 1, first paragraph). The results of prolactin levels of schizophrenic patients receiving 3 mg of risperidone (*i.e.*, "low dose" as defined by Applicants' own specification – see paragraph 0019 on page 2) are shown in Figure 1 on page 134, and show the largest increase in prolactin levels at low dosages.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Suzuki #1, Suzuki #2 and Turrone is directed towards treating schizophrenia. One of ordinary skill in the art would have understood the advantages of using a genetic screening based on A1+ allele determination for drug administration because Suzuki #1 shows that nemonapride, a drug that binds highly with DRD2, is substantially more effective in treating patients with the A1+ allele than the A1- allele. Based on the relationship between dosages illustrated by Suzuki #2 and Turrone, one of ordinary skill in the art would have had the requisite guidance for dosage administration, and understood how drugs, like nemonapride and clozapine, having different therapeutic effects based on the A1

allele, and are useful to treat symptoms of schizophrenia. Therefore, the invention as a whole was *prima facie* obvious at the time it was made.

Claims 1, 2, 5 and 6, are obvious over Suzuki #1, Suzuki #2, Turrone and Bourin:

Claims 1, 2, 5 and 6, are rejected under 35 U.S.C. 103(a) as being unpatentable over Suzuki #1, Suzuki #2 and Turrone, as applied to claims 1, 2 and 5 above, and further in view of Bourin *et al.*, *CNS Drug Reviews 7(1)*:25-47 (**2001**).

The limitations of claims 1, 2 and 5, and the corresponding teaching of the art, are found in the rejection above and are hereby incorporated into the instant rejection.

As required by claim 6, neither Suzuki #1, Suzuki #2 or Turrone explicitly suggest to use paroxetine.

Bourin provides a review article on paroxetine, a compound for treating depression and anxiety, and teaches that is considered a well-tolerated drug (page 26, third paragraph in the section *Introduction*), discloses that it is one of the most potent inhibitor of 5-HT reuptake of available antidepressants (page 27, third paragraph), and that the compound does not interact with the dopamine D2 receptor:

> "Both, in vitro and in vivo studies have demonstrated that paroxetine is devoid of any significant affinity for adrenoceptors (α1, α2, β), dopamine (D2) receptors, histamine (H1) receptors, or 5-HT receptor subtypes (5-HT1A, 5-HT2)."

Bourin, page 28, third paragraph.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of the references are directed to psychiatric treatment of psychotic and/or psychiatric disorders. One of ordinary skill in the art would have recognized that due to the safety and success in treatment with paroxetine, that monitored treatment with paroxetine in addition to low dose binding DRD2 binding agents would provide added treatment for anxiety and/or depression that often accompanies many psychotic disorders, such as schizophrenia. Therefore, the invention as a whole was *prima facie* obvious at the time it was invented.

Common Ownership of Claimed Invention Presumed

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. §§ 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Conclusions

No claim is allowable.

If Applicants should amendment the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jeffrey S. Lundgren/
Patent Examiner, Art Unit 1639